ReGen Biologics, Inc.
Collagen Scaffold (CS)

Orthopedic and Rehabilitation Devices
Advisory Panel Meeting
March 23, 2010

FDA Presenters:
Elizabeth Frank, M.S.
Srinidhi Nagaraja, Ph.D.
Elizabeth Adegboyega-Panox, M.D.
Scott Miller, Ph.D.

Overview

- Reason for Panel Meeting
- Device Overview
- Substantial Equivalence Decision Making Process
- Predicate Device Information
- Pre-Clinical Information
- Clinical Protocol
- Safety/Effectiveness Evaluation
- Statistical Analysis
- Panel Questions

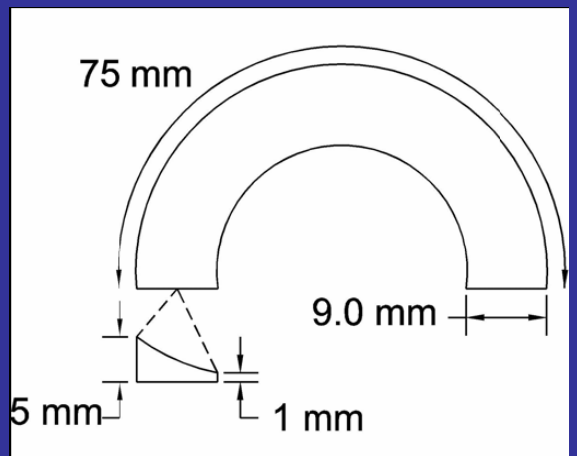
Cleared Indications for Use

The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the medial meniscus. In repairing and reinforcing medial meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure.

Device Description

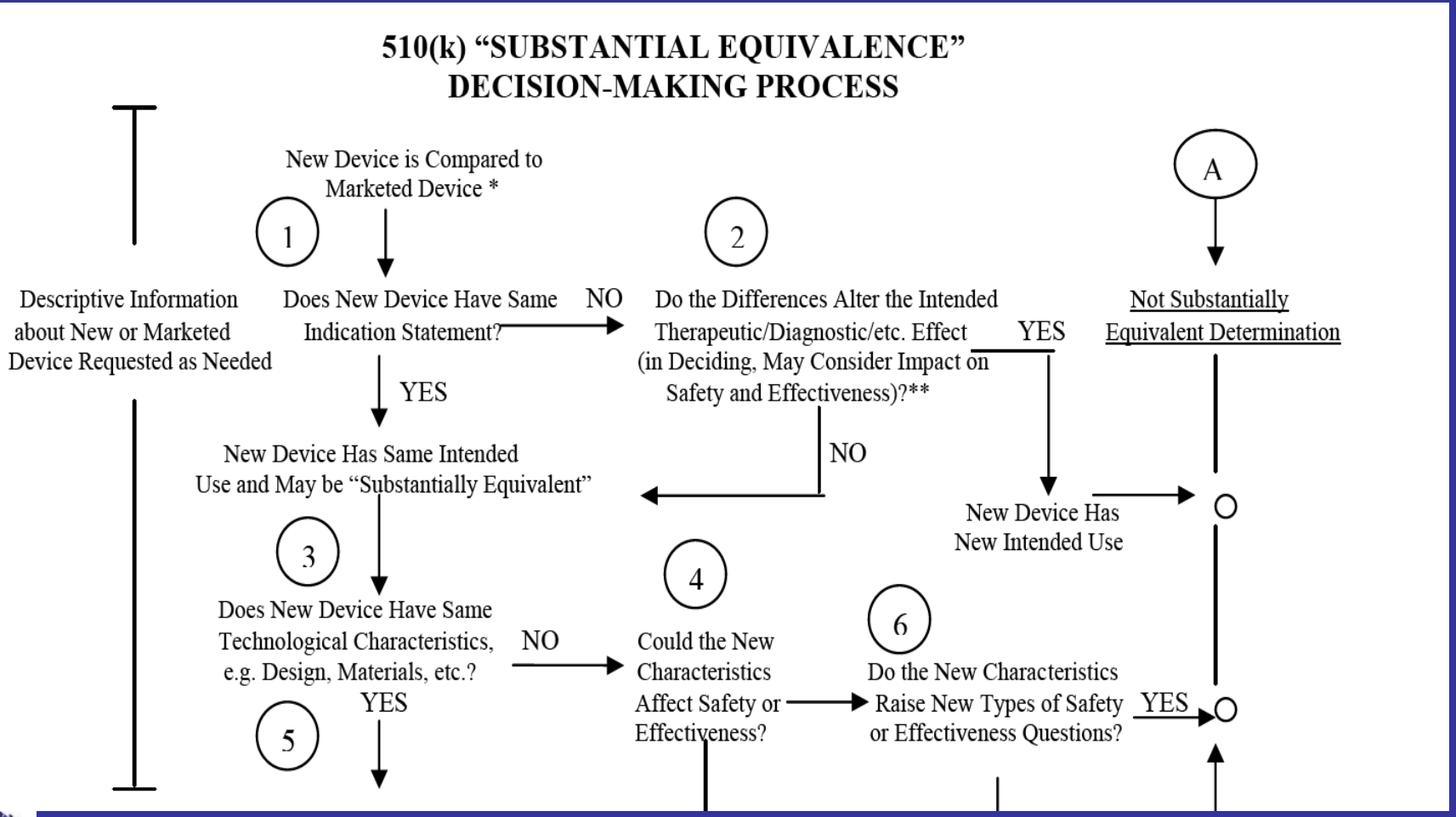
- Resorbable matrix composed of Type I Collagen
- Semi-lunar shape with a triangular cross-section for use in meniscus
- Surgeon trims device to size necessary for repair of damaged or weakened soft tissue
- Sutured in place through a minimally invasive arthroscopic procedure



Substantial Equivalence Decision Making Process

- The 510(k) Flowchart is a decision making tool based on the applicable laws and regulations that CDRH uses to determine whether or not a device is substantially equivalent to a legally marketed device.
- A copy of the 510(k) Flowchart has been provided in Attachment D of the FDA Executive Summary

510(k) Flowchart



Surgical Meshes

- The Regen CS device was cleared as a Surgical Mesh.
- Surgical Mesh devices defined in 21 CFR § 878.3300
  - Title 21 – Food and Drugs
  - Part 878 – General and Plastic Surgery Devices
  - Section 878.3300 Surgical Mesh:

    (a) Identification. Surgical mesh is a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are metallic and polymeric mesh for hernia repair, and acetabular and cement restrictor mesh used during orthopedic surgery.

    (b) Classification. Class II.

Orthopedic Predicate Devices

DePuy Restore ® Surgical Mesh (K031969)

Indications for Use:

"Is intended for use in general surgical procedures for reinforcement of soft tissue where weakness exists. In addition, the implant is intended for use in the specific application of reinforcement of the soft tissues, which are repaired by suture or suture anchors, during rotator cuff repair surgery.

The Restore® Implant is not intended to replace normal body structure or provide the full mechanical strength to repair the rotator cuff. Sutures to repair the tear and suture or bone anchors to reattach the tissue to the bone provide mechanical strength for the rotator cuff repair. The Restore® Implant reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue."

Orthopedic Predicate Devices

DePuy Restore ® Surgical Mesh (K031969) (cont.)

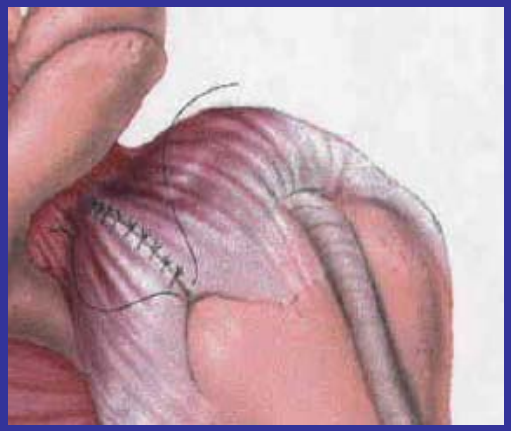
Excerpt from Surgical Technique:

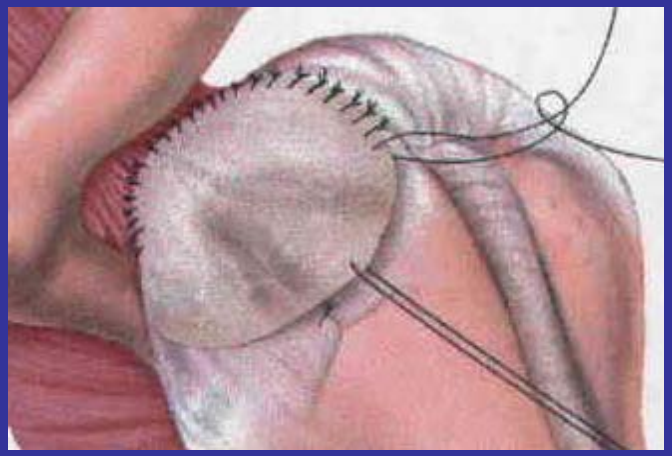
> "Once the cuff repair has been completed [suture or suture anchor repair], in order to create a smooth area for muscle articulation over the Rotator Cuff Repair, a hydrated Restore Orthobiologic Soft Tissue Implant may be placed over the soft tissue portion of the repair"

Orthopedic Predicate Devices

DePuy Restore ® Surgical Mesh (K031969) (cont.)

Pictures from DePuy Restore Surgical Technique Guide:





Orthopedic Predicate Devices

TEI Bio-sciences OrthoMend / TissueMend (K051706)

- OrthoMend Soft Tissue Repair Matrix is intended for reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons.

- OrthoMend Soft Tissue Repair Matrix is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Sutures used to repair the tear and sutures or bone anchors used to attach the tissue to the bone provide biomechanical strength for the tendon repair. OrthoMend Soft Tissue Repair Matrix reinforces soft tissue and provides a remodelable scaffold that is replaced by the patient's own soft tissues.

Comparing the Use of Rotator Cuff Surgical Meshes with the ReGen Collagen Scaffold

- The rotator cuff stabilizes and supports the shoulder joint. The mesh is not located within the intra-articular joint space.
- The use of a surgical mesh in rotator cuff repair is to create a smooth area over a sutured repair; it is not for use in a fully weight-bearing joint or to provide additional mechanical strength to the repair
- Differences in the loading profile between the knee and shoulder

Additional Predicate Devices

Surgical meshes have been cleared to reinforce soft tissue where weakness exists in a variety of anatomical locations, such as:

- hernia;
- anal, rectal and enterocutaneous fistulas;
- urethral and vaginal prolapse repair;
- colon and rectal prolapse repair;
- reconstruction of the pelvic floor;
- bladder support;
- soft tissue of the lung, etc.

Additional Predicate Devices

Cook Biotech, Inc. SIS Fistula Plug (K050337)

- The SIS Fistula Plug is for implantation to reinforce soft tissue where a rolled configuration is required, for repair of anal, rectal, and enterocutaneous fistulas. The device is supplied sterile and is intended for one-time use.

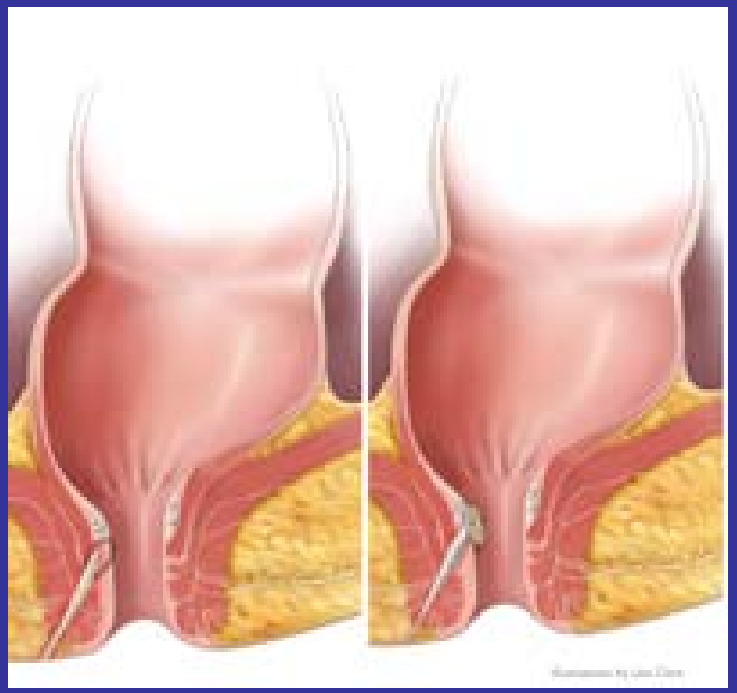
Additional Predicate Devices

Cook Biotech, Inc. SIS Fistula Plug (K050337)

- The mesh is provided in sheet form
- The sheet is rolled and implanted
- The implanted device acts as a seton providing to drainage to the exterior of the body
- Loading profile unknown

Additional Predicate Devices

Cook Biotech, Inc. SIS Fistula Plug (K050337)



Differences in Technological Characteristics

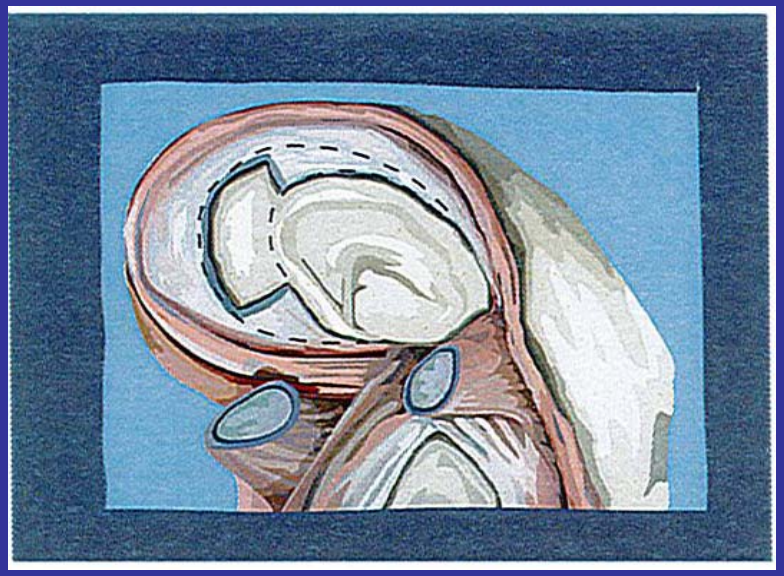
- When comparing a new device to predicate devices the technological characteristics of the devices are considered. Some of the key characteristics that are considered for the proposed indications for use are:
  - Material
  - Shape
  - Size/dimensions
  - Anatomical location
- Panel will be asked to comment on these differences between the CS device and the referenced predicate devices

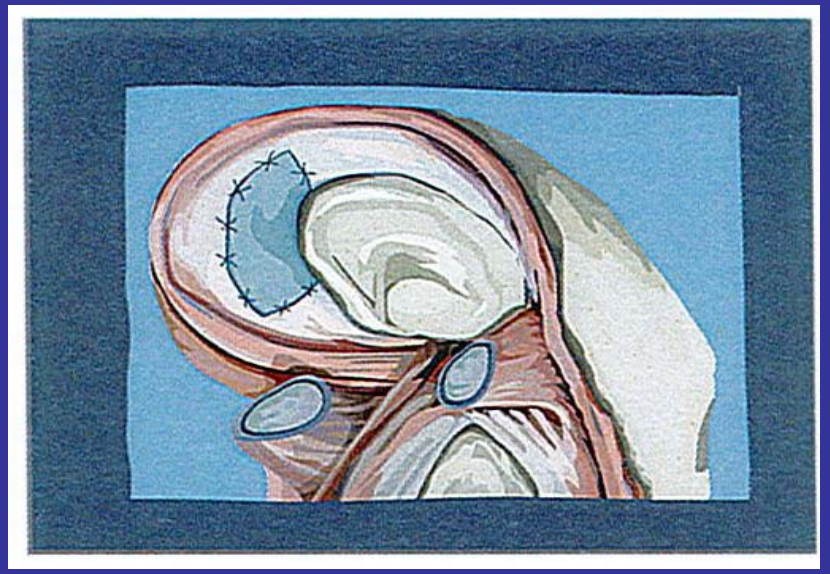
Performance Data

- Evaluate bench, animal and/or clinical data
- Ensure level playing field
- Ensure confidentiality of data

Availability of Appropriate Performance Data

Are the performance data appropriate to assess the proposed indications for use?





How does the ReGen CS device reinforce and repair soft tissue injuries of the medial meniscus?

Considerations for Appropriate Performance Data

- IDE enrollment criteria
  - Irreparable injury
- Surgical mesh definition (§ 878.3300)
  - Reinforce soft tissue or bone where weakness exists
- Quantity of excised tissue
  - Is repair possible?
  - 43% (37/87) of chronic subjects had at least 80% of the meniscus removed
  - 72% (63/87) of chronic subjects had 50% or more of the meniscus removed

ReGen Collagen Scaffold Pre-Clinical Testing

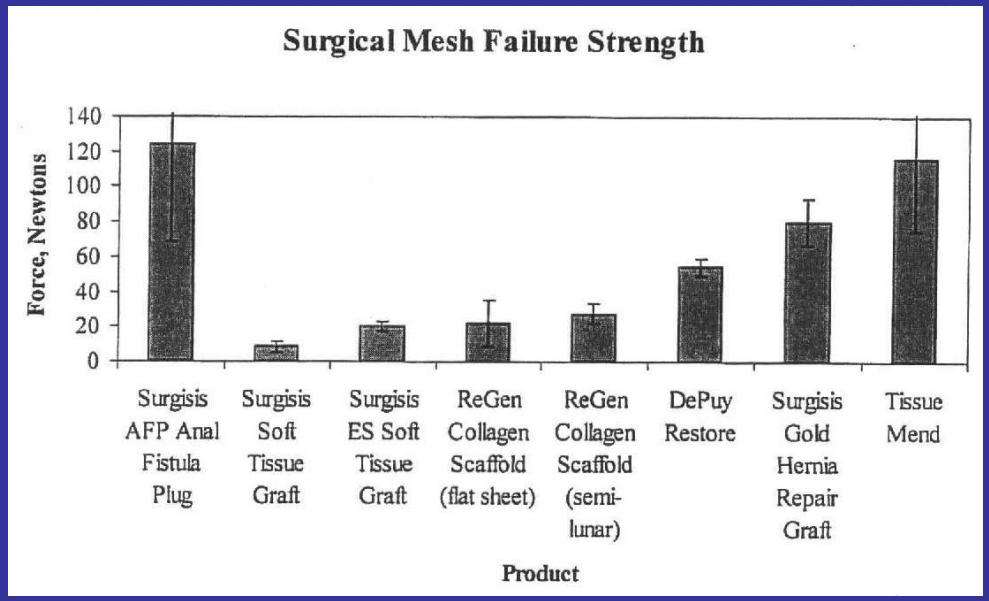
Srinidhi Nagaraja, PhD
Mechanical Engineer
Office of Science and Engineering Laboratories
CDRH/FDA

Pre-Clinical Information

- Suture Retention Strength
- Tensile Strength
- Biomechanics of the Meniscus and Stresses in the Shoulder
- Animal Testing
- Biocompatibility
- Virus Inactivation
- Sterilization
- Packaging and Shelf Life

Tensile Strength

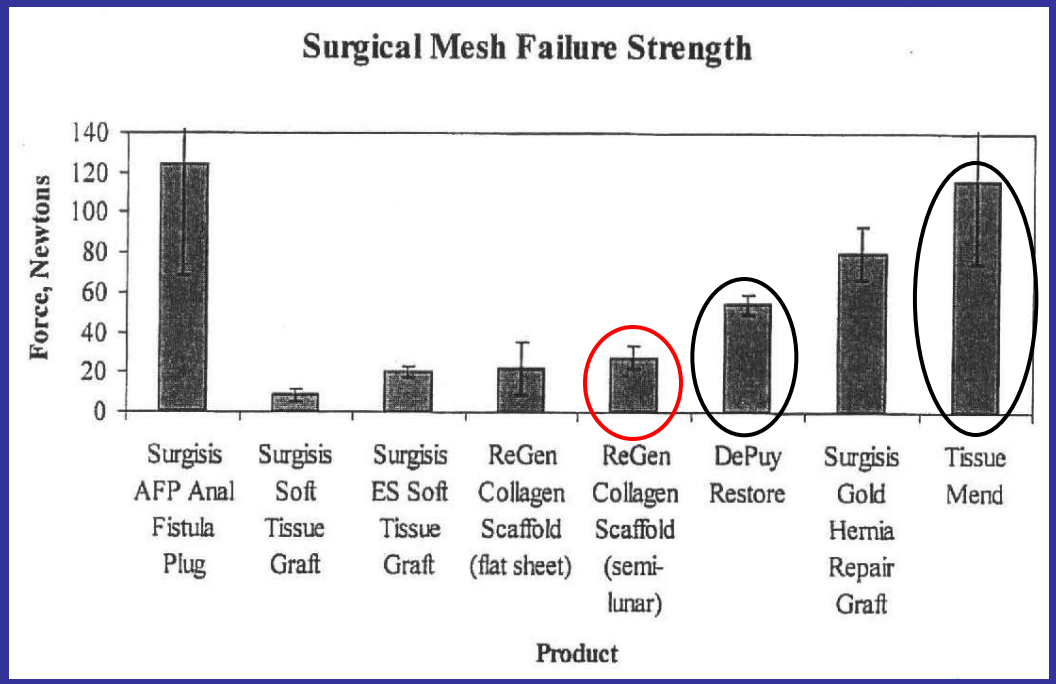
- CS device and 6 predicate meshes tested (n=3 per group)
- Orthopaedic → Depuy Restore and TissueMend
- Non-orthopaedic → Surgisis AFP, Soft Tissue Graft, ES Soft Tissue Graft and Gold Hernia Repair Graft



Sponsor conclusion → CS device falls well within the range of mechanical strengths exhibited by technologically similar devices having the same intended use

Tensile Strength - FDA Analysis

- ReGen stated that shoulder surgical meshes are the most comparable predicates from a biomechanical perspective
- CS device has significantly decreased failure force relative to the Restore and TissueMend devices ($p<0.05$, FDA analysis)
- A non-parametric Kruskal-Wallis test is more appropriate, but requires data from individual samples which ReGen did not submit



Biomechanics of the Meniscus

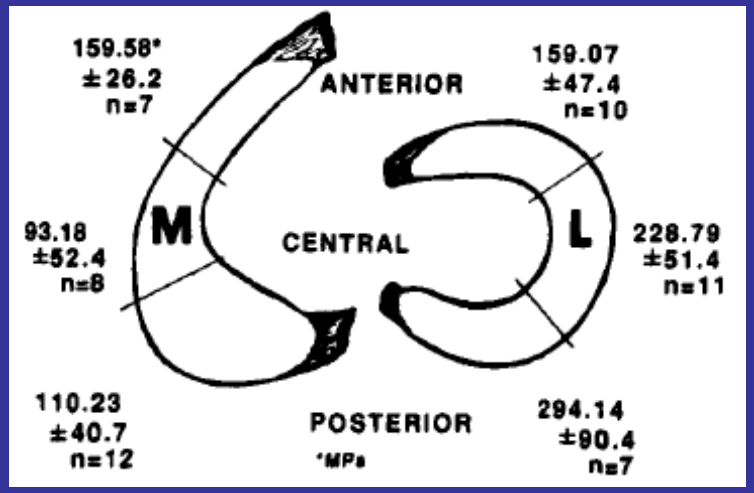
Sponsor Analysis

- Mean tensile stress of 350 kPa on the meniscus (n=3) (Krause et al 1976)
- Tensile testing of CS device
  - CS device sutured to bovine meniscus (n=3)
  - Mean tensile strength of 560 kPa
- Sponsor conclusion → CS device has adequate reinforcement to the native meniscus at the time of placement

Biomechanics of the Meniscus

FDA Analysis

- Krause et al: circumferential stress (350 kPa) calculated by assuming a tissue modulus (E) of 18 MPa ($\sigma = E^*\varepsilon$)
- Recent study reported tissue moduli ranging from 93 -294 MPa in the circumferential direction (Fithian et al 1990)



From Fithian et al

- Re-calculated stresses within the medial meniscus would be 5-9X greater (1750-3150 kPa) than the referenced 350 kPa

Biomechanical Comparison of Meniscus to Shoulder

Sponsor Analysis

- ReGen used reported shoulder joint reaction force of 337N (Parsons et al 2002) to obtain a stress of 2800 kPa
- ReGen concluded that “the calculated primary force of tension in the shoulder of 2800 kPa is nearly an order of magnitude greater than the primary force of tension reported for the meniscus of 350 kPa”
- ReGen stated “use of the device in the meniscus does not present new types of safety or effectiveness questions as compared to its predicates, in particular the Restore device”

Biomechanical Comparisons

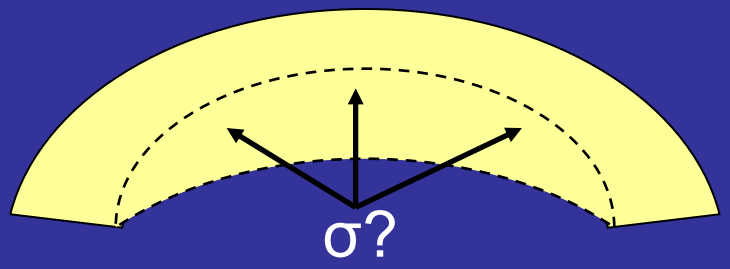
FDA Analysis - Shoulder Stresses

- Reported shoulder forces are counteracted by several muscles and tendons that surround the shoulder joint
- Predicate shoulder meshes are not intended to replace normal body structure or provide full mechanical strength to repair the rotator cuff
- Sutures and bone anchors provide the primary biomechanical strength for the tendon repair
- FDA Concern → calculated joint stress of 2800 kPa does not estimate stresses that a rotator cuff repair device would experience

Biomechanical Comparisons

FDA Analysis – Meniscal Stresses

- More accurate estimates of meniscal stresses may be available from newer scientific data published after 1976 Krause article
- Are there significant stresses in areas of the meniscus where the CS device is intended for implantation?



Summary - Mechanics

- Tensile strength performance data → difficult to compare strengths of meshes indicated for different anatomical locations
- Biomechanical comparisons → Stresses reported for shoulder and meniscus are based on several assumptions
  - Limits ability to make accurate comparisons
- Do the performance data submitted demonstrate that the CS device can withstand loads/stresses expected in the inner meniscus?

Animal Study Design

- 80% removal of canine medial meniscus
- Replacement with CS device
- Gross observations of knee joints
- Histopathology → hematoxylin and eosin (H&E)

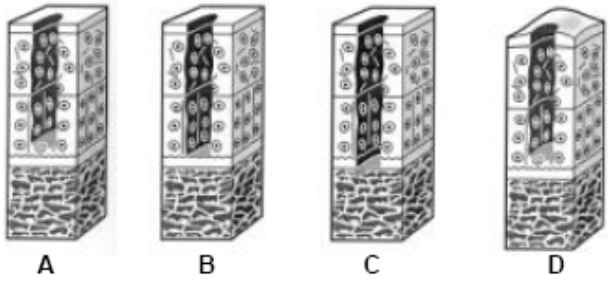
# of Dogs	Experimental Knee	Control Knee	Duration
2	4	None	3 weeks
2	4	None	6 weeks
2	4	None	12 months
1	2	None	13 months
2	4	None	17 months
Total **9**	**18**	**0**	

Knee Joint Observations

- 15/18 knee joints → good or excellent tissue appearance
- Long term (≥12 months) → 7/10 small kissing lesions on tibia or femur
- 5/10 long term knees → ICRS Grade 3-4 (severely abnormal) on opposing femur and/or tibial surfaces

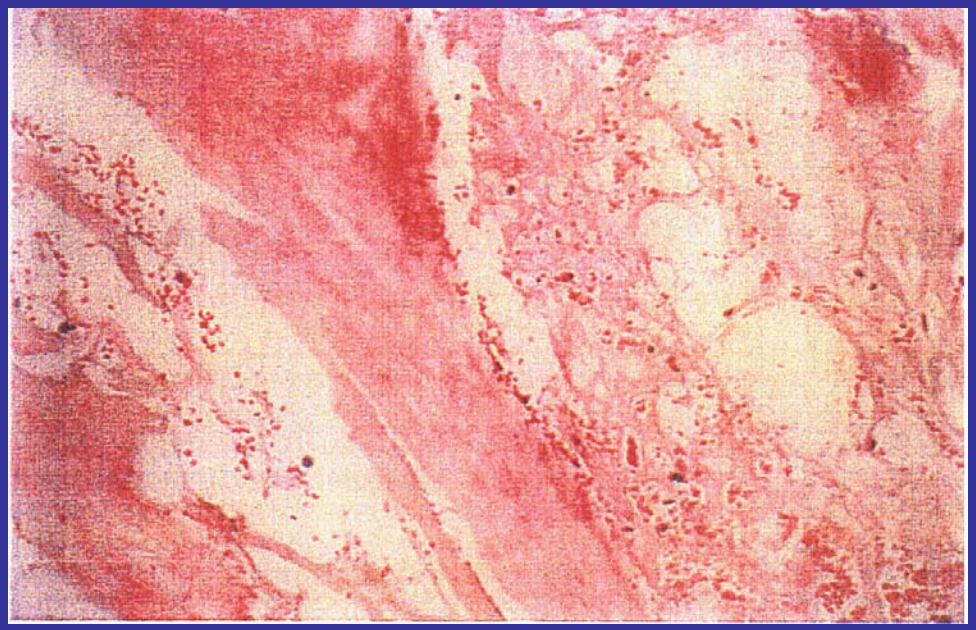
ICRS Grade 3 – Severely Abnormal

Cartilage defects extending down >50% of cartilage depth (A) as well as down to calcified layer (B) and down to but not through the subchondral bone (C). Blisters are included in this Grade (D)

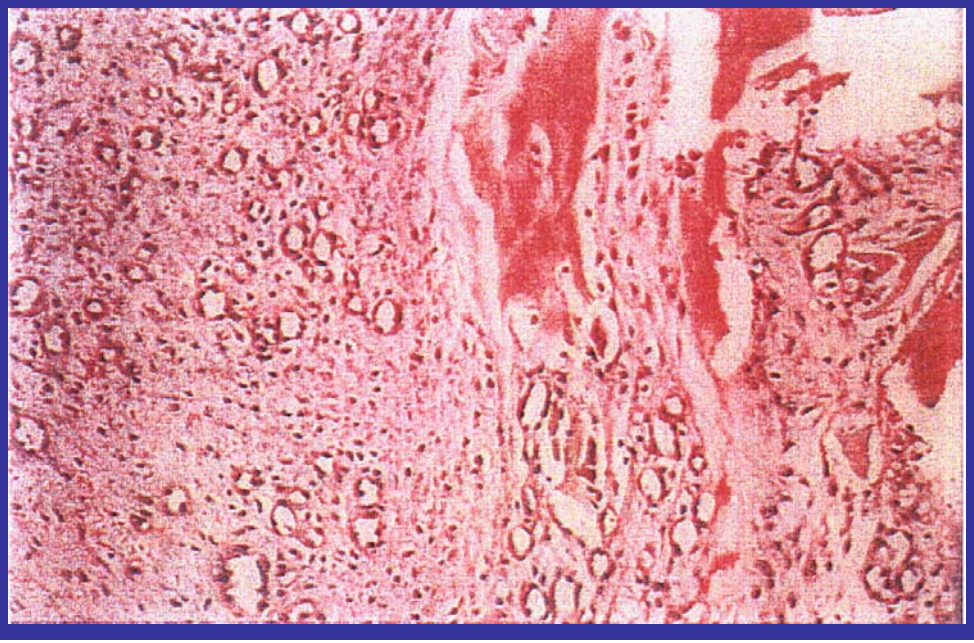


- FDA Concerns → No documentation (images/details) to characterize lesions and no control knees for comparisons

Animal Study – Histology (H&E)

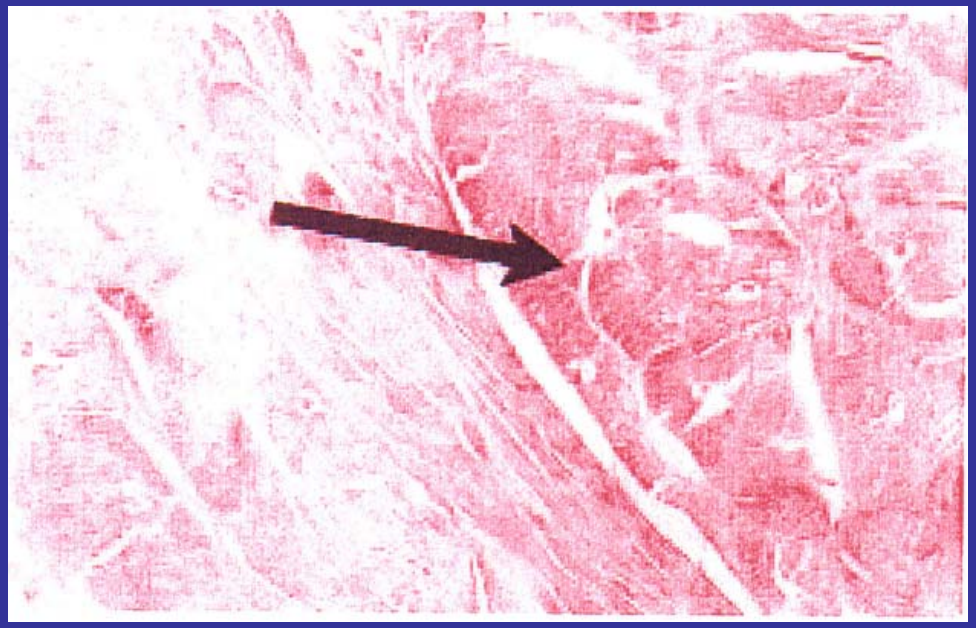


3 weeks

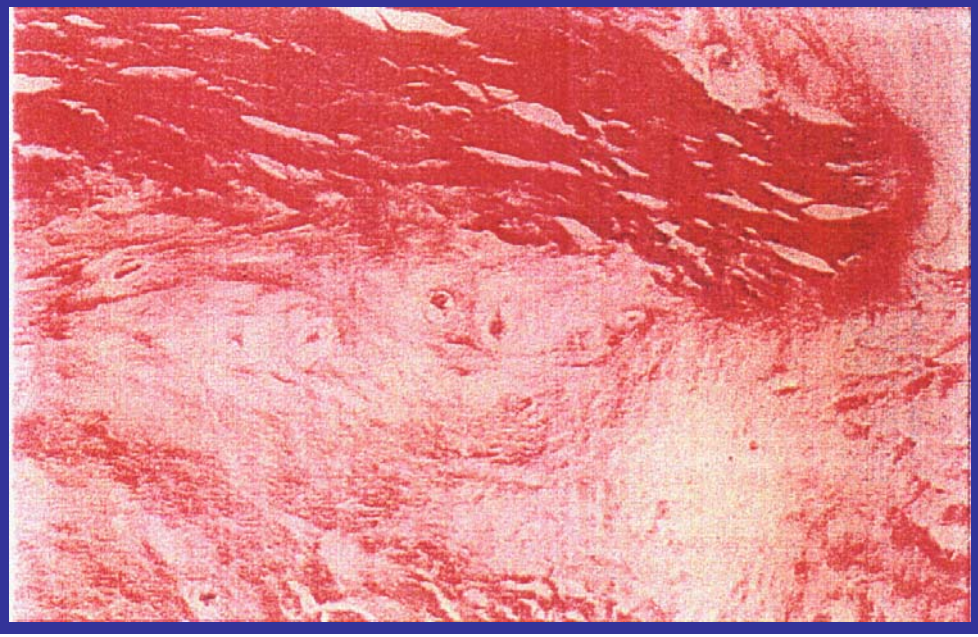


6 weeks

Animal Study – Histology (H&E)



12 months



17 months

Animal Study - Grading

Tissue Phases

Grade 1: Fibrin clot
Grade 2:Vascular proliferation (angiogenesis) and cellular (granulation tissue type) proliferation
Grade 3: More dense matrix and connective tissue
Grade 4: Fibrochondrocytic tissue

CS Extracellular Matrix

Grade 1: No new connective tissue matrix
Grade 2: Random fibrous connective tissue
Grade 3: Organizing fibrous connective tissue
Grade 4: Fibrocartilaginous tissue

Angiogenesis

Grade I: None
Grade 2: Mild
Grade 3: Marked

	3 Weeks	6 Weeks	1 Year	1.5 Years
Tissue Phases 1-4	1.2	2.0	4.0	4.0
Extracellular Matrix 1-4	1.2	2.3	4.0	4.0
Angiogenesis 0-3	1.2	3.0	0.5	0.0

Animal Study - Grading

Cellular Resorption of the CS device

Grade 1: None
Grade 2: 1-25%
Grade 3: 25-50%
Grade 4: >50%

CS Appearance

Grade 1: Broad smooth bands present
Grade 2: CMI discontinous and thinning
Grade 3: >50% of the CMI thinned and irregular

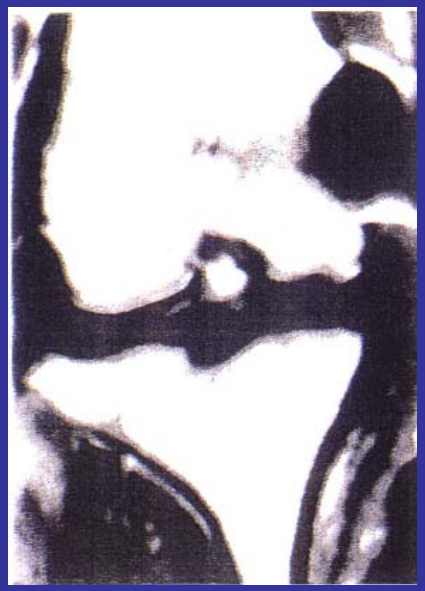
CS Host Integration

Grade 1: None
Grade 2: Focal
Grade 3: Moderate
Grade 4: Marked

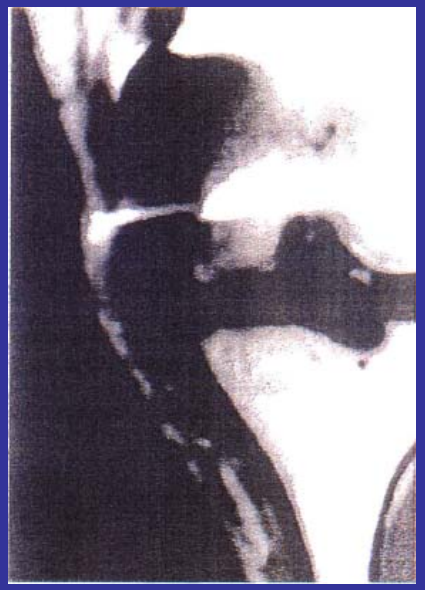
	3 Weeks	6 Weeks	1 Year	1.5 Years
Cellular Resorption of CS 1-4	2.2	1.4	1.2	1.0
CS Appearance	1.4	1.3	2.9	2.7
CS/Host Integration	1.0	1.0	3.5	4.0

MRI Evaluation of Tissue Ingrowth

MRI (1.5 T) performed on 18 of 24 dog knees



3 weeks



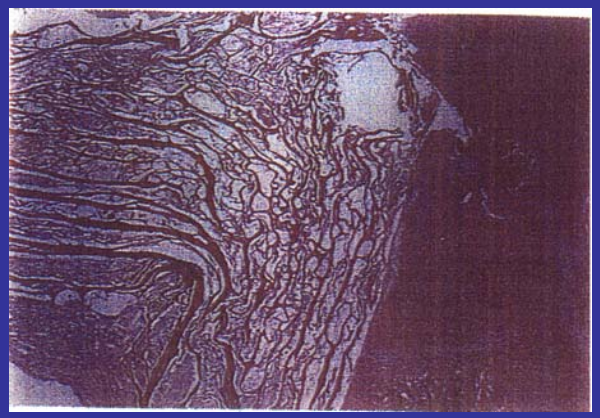
6 weeks

6 months

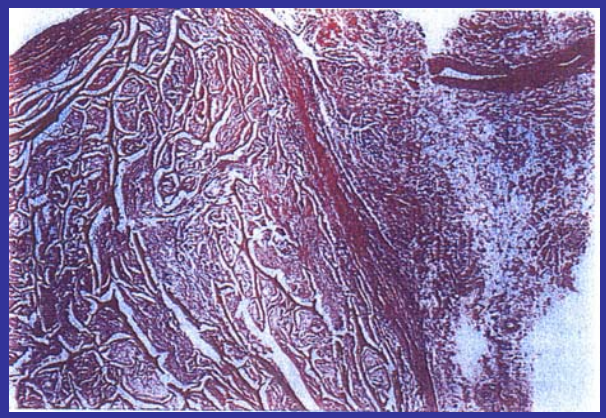
"The MRI findings did not appear to show a clear progression of tissue maturity from 3 weeks to 3 months, although the 6 month MRI showed a possible progression of tissue maturity" – Dr. Ho

MRI Evaluation of Tissue Ingrowth

After MRI evaluation 20 specimens were histologically evaluated (H&E)



3 weeks



6 weeks

6 months

"There clearly is a maturity progression from 3 weeks to 6 weeks and from 3 months to 6 months. Somewhat surprisingly, there is still a large amount of the implant remaining even at 6 months" - Drs. Arnoczky and Rodkey

Summary - Animal Study

- H&E → Difficult to distinguish between the collagen scaffold and the host tissue
- Quality of tissue being formed is not well understood → GAG content and collagen type
- At 6 weeks (patient becomes fully weight bearing)
  - No host integration into CS device
  - Extracellular matrix is comprised of random fibrous connective tissue
  - No observations of a dense matrix of connective tissue
- FDA Concerns
  - Information provided is unclear or conflicting
  - Tissue formation by 6 weeks may not provide structural support when patient becomes weight bearing
  - Grade 3-4 lesions on articular surfaces of the femur and tibia → CS device or newly formed tissue may damage adjacent cartilage

ReGen Collagen Scaffold
Clinical Data

Elizabeth Adegboyega-Panox, M.D.
Medical Officer
OSDB/DSORD/Office of Device Evaluation

Study Design

- Randomized
- Prospective
- Controlled
- Unblinded
- Multicenter

Intended Use

The device is intended to reinforce soft tissue where a weakness exists by addition of a scaffold which is ultimately replaced by the patient's own tissue which functions to permanently reinforce the defect by replacing lost tissue volume.

Indications for Use

K082079

The Regen Collagen Scaffold is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the medial meniscus. In repairing and reinforcing medial meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure.

Patient Populations

Two Study Arms	Control
"ACUTE" No previous meniscal surgery	Partial Meniscectomy
"CHRONIC" 1-3 previous meniscal procedures	

Key Inclusion Criteria

- Diagnosis of meniscus tear confirmed by MRI
- Concomitant ACL injury stabilized within 12 weeks of index procedure
- Degenerative change limited to Grade I-III in medial and P-F compartments

Key Exclusion Criteria

- Concomitant injury to contralateral limb
- Concomitant lateral meniscal injury in ipsilateral limb
- Concomitant PCL insufficiency or injury
- Grade IV (most severe) degenerative change in any compartment of the knee
- Allergy/Anaphylactoid reaction to collagen of animal origin

Surgical Technique

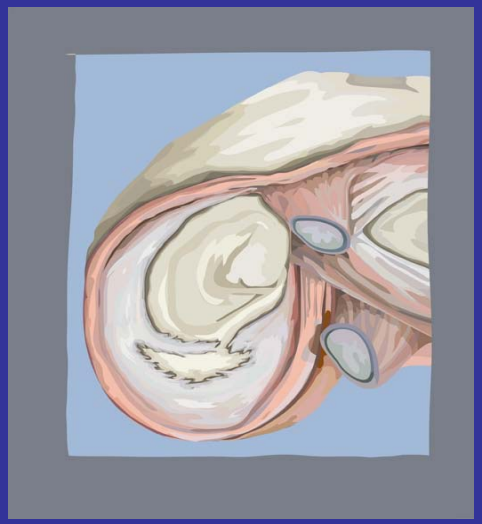
- Both Control and Study Patients:
  - Arthroscopic assessment of meniscal lesion and joint
  - Partial meniscectomy
  - ± Prophylactic antibiotics
  - PRN analgesics
- CS Patients:
  - Site preparation
  - Measurement of length of defect and height of residual rim
  - Device sized to these dimensions
  - Device sutured into place

Meniscus Defect Criteria

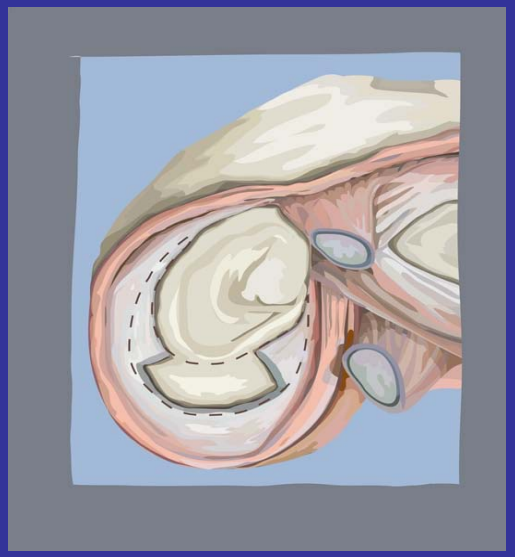
- Irreparable injury
- Traumatic or degenerative origin
- Intact anterior and posterior horns
- Site prep results in full thickness defect
- Site prep results in extension into vascular zone of peripheral meniscus
- Intact meniscal rim

Surgical Procedure

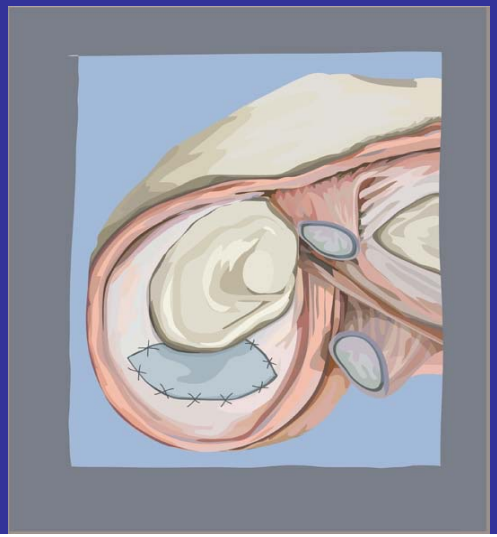
1



2



3



Post-operative Rehabilitation

- CS Patients
  - NWB + Passive ROM x 1 week
  - PWB + Passive ROM x 5 weeks
  - WBTT beginning at 6 weeks and progressing to Full Activity at 6 months
- Control
  - Less formal rehab
  - RTW in 2-3 weeks

Study Endpoints

- Safety
  - Blood analysis
  - Adverse events

Study Endpoints

- Effectiveness
  - Arthroscopic appearance
  - Histopathology
  - Pain
  - Swelling
  - Lysholm Knee Activity score
  - Patient functional self assessment

Study Endpoints

- Other
  - Synovial fluid analysis
  - Redness
  - Skin/superficial wound infection
  - Range of motion
  - Thigh girth measurement
  - Tegner Activity Level
  - Radiographic evaluation

Study Endpoints

- Other
  - Gross appearance of regeneration
  - Gross appearance of implant
  - Implant host stability
  - Presence of loose bodies or fraying
  - Implant host junction (separation/integration)
  - Presence of inflammatory response

Success Definition

- Individual patient success – Clinically significant improvement in 2 of 3 of the following:
  - Pain
  - Lysholm scale of knee function
  - Patient functional self assessment

Patient Accounting

Patients	Number
Assessed for Eligibility	494
Enrolled	311
Excluded	183
Withdrew before Surgery	49
Other	2

Patient Accounting

	Acute	Chronic
Total N	157	154
CS	75	85
Control	82	69
Lost to Follow-Up	0	0
Withdrawn	0	3
Early Infection	-	1
Death	-	2
Analyzed	157	151
Excluded from Analysis	0	3

Patient Withdrawal
(N=49)

Device (15)		Control (34)	
Acute Arm	5	Acute Arm	9
Chronic Arm	10	Chronic Arm	25

Patient Accountability
Pooled "Chronic" and "Acute" Arms

	Patient Follow-Up	6 Weeks	6 Months	12 Months	24 Months	> 24 Months
CS (N=162)	Theoretical*	161	157	152	146	142
	Actual**	160 (99%)	153 (97%)	142 (93%)	132 (90%)	130 (92%)
Control (N=151)	Theoretical*	147	144	140	134	132
	Actual**	127 (86%)	125 (87%)	121 (86%)	128 (96%)	121 (92%)
Overall (N=313)	Theoretical*	308	301	282	280	274
	Actual**	287 (93%)	278 (92%)	263 (90%)	260 (93%)	251 (92%)

* Patients available for follow-up (excludes: explants, deaths, confirmed lost to follow-up, withdrawals, and excluded other than at surgery)

Patient Accounting

	Baseline	24 Months
CS Device	162	132 (81.5%)
Control	151	128 (84.8%)

Patient Accounting
"Chronic" Arm

	6 Weeks	6 Months	24 Months	48 Months	84 Months
Theoretical (Calculated)	86	82	80	66	35
Actual	85	80	68	27	18
Lost to Follow-up	0	0	1	2	2
Excluded	0	0	2	2	2
Withdrawals	0	0	1	1	1
Not Yet Due	0	0	0	14	45
Explants	1	5	5	5	5
Deaths	0	0	2	2	2
Percent Follow-Up	99%	98%	85%	41%	51%

Demographics

	Acute (N=157)		Chronic (N=154)	
	CS	Control	CS	Control
Patients enrolled and evaluated	75	82	85	69
Concurrent ACL Reconstruction	22	16	25	22
Follow-up time (months)				
Range	23-89	16-85	23-90	23-92
Mean	64	60	60	57
Mean Age (years)	40	40	38	39
Sex				
Male	65	67	61	50
Female	10	15	24	19

There were no significant differences between the treatment groups within the study arms.

Results - Safety
Adverse Events

	CS	Control
Serum Analysis (ELISA Antibodies)	Not statistically significantly different	
ADVERSE EVENTS		
Serious AEs		
Total Events/Total Patients	37/87	23/69
Events per Patient/Total Patients	21/87	14/69
Serious Device Related AE		
Total Events/Total Patients	14/87	2/69
Events per Patient/Total Patients	8/87	1/69

Results - Safety
Adverse Events

	CS	Control
Non-Serious Device Related AE		
Total Events/Total Patients	51/87	5/69
Events per Patient/Total Patients	29/87	3/69
Non-Serious AE		
Total Events/Total Patients	241/87	201/69
Events per Patient/Total Patients	71/87	49/69
All AE		
Total Events/Total Patients	295/87	240/69
Events per Patient/Total Patients	74/87	54/69

Results – Safety
Adverse Events (JBJS)

- Classification as serious or clinically relevant is by the surgeon investigator, and required some form of treatment

Patient Population	Number of AEs
CS Device	11
Control	10

Results – Safety
Adverse Events

Complication	CS	Control
Pain	2	7
Swelling/Effusion	4	1
Instability	1	0
Infection/Fever	1	1
DVT	1	1
Wound Related	1	0
P-F Symptoms	1	0

Explants

Patient	Time Post-Op	Reason
#1	3 weeks	Infection. Felt by surgeon to be seeded from medial incision that was slow to heal.
#2	3 months	Persistent pain and swelling after device placement. Mechanical Failure of implant. Device failed at midpole, was fragmented and resorbed.
#3	4 months	Excessive pain. Mechanical Failure. Histology: Meniscal tissue is not present.
#4	4 months	Subject used treadmill leading ot Mechanical Failure.
	6 months	Implant Failure. Explanted due to severe pain and swelling.
#5	6 months	Patient fell prior to the 6-wk post-operative time point. Patient complained of increased pain and laxity of the joint after the fall. Patient had explant due to Mechanical Failure and PCL shrinkage.

Results – Effectiveness

Pain at 24 months (VAS Scale 0-100)

Treatment Group	Pre-Operative	24 Months	Change from Baseline
CS Device	35 ± 24 (N=155)	12 ± 16 (N=132)	22 (N=131)
Partial Meniscectomy	37 ± 24 (N=149)	11 ± 16 (N=130)	25 (N=129)

Results – Effectiveness

Pain at longest follow-up (VAS Scale 0-100)

Group	Mean VAS Score Pre-Op.	Mean VAS Score at Longest Follow-up	Change in Mean VAS Score
Chronic CS Patients	38 (N=86)	19 (N=77)	17 (N=76)

Results – Effectiveness
Function

- Lysholm Score (0-100) at 24 months

Treatment Group	Pre-Operative	24 Months	Change from Baseline
CS Device	63 ± 19 (N=156)	86 ± 17 (N=133)	23 (N=133)
Partial Meniscectomy	59 ± 21 (N=151)	86 ± 15 (N=130)	27 (N=130)

Results – Effectiveness
Function

- Change in Lysholm Score from baseline to longest follow-up

Group	Mean Lysholm Score Pre-Op.	Mean Lysholm Score at Longest Follow-up	Change in Lysholm Score at Longest Follow-Up
Chronic CS Patients	62 (N=87)	78 (N=77)	16 (N=77)

Results – Effectiveness

Patient Satisfaction

	Pre-op	Longest Follow-Up
Dissatisfied/ Somewhat Dissatisfied	91%	30%
Satisfied/ Somewhat Satisfied	1%	63%

Results – Effectiveness
Functional Self-Assessment

Treatment Group	Status	Pre-Op	24 Months
		N=156	N=133
CS Patients	Normal	6 (4%)	62 (47%)
	Nearly Normal	62 (40%)	62 (47%)
	Abnormal	81 (52%)	8 (6%)
	Severely Abnormal	7 (4%)	1 (1%)

Results – Effectiveness
Functional Self-Assessment

Treatment Group	Status	Pre-Op	24 Months
		N=151	N=130
Partial Meniscectomy Patients	Normal	1 (1%)	56 (43%)
	Nearly Normal	54 (36%)	65 (50%)
	Abnormal	72 (48%)	7 (5%)
	Severely Abnormal	24 (16%)	2 (2%)

Results – Effectiveness

- Patient functional self-assessment change from baseline to longest follow-up

Treatment Group	Change from Baseline
CS Device	0.94 (N=133)
Control	1.12 (N=130)
p-value	0.10

Results – Effectiveness
Activity

- Tegner Score and Index at longest follow-up

Group	Pre-Injury Tegner Score	Pre-Op Tegner Score	Tegner Score at Longest Follow-Up	Tegner Index at Longest Follow-Up
Chronic CS Patients	6.5 (N=87)	2.8 (N=87)	4.2 (N=77)	0.4 (N=74)

Results – Effectiveness
Tissue Gain

- At index surgery percent meniscal tissue remaining:

	Subjects Receiving Device	Control
Acute	52%	59%
Chronic	36%	40%

Tissue Gain

Initial Surgery	
N	Percent Meniscus Remaining Mean (SD)
87	37% (20)

Relook Surgery		
N	Total Tissue Mean (SD)	Percent Tissue Gain
76	73 (20)	97%

Results – Effectiveness

Percent Total Tissue at Re-look

Protocol	Treatment Group	N Observed (N Missing)	Percent Tissue Loss (SD)	N Observed (N Missing)	Percent Tissue Total at Re-Look (SD)
Acute	CS	75 (0)	48 (20)	65 (10)	74 (17)
	Control	83 (1)	41 (20)	NA*	59*
Chronic	CS	87 (0)	64 (20)	76 (11)	73 (21)
	Control	66 (1)	60 (22)	NA*	40*
Overall	CS	162 (0)	57 (22)	141 (21)	73 (19)
	Control	149 (2)	50 (23)	NA*	50*

Effectiveness - Biopsy of Tissue

- 136 biopsies were performed
- 81 assessed for cellular response (contained residual device)
  - Marked cellular ingrowth 94%
  - Extracellular matrix to some degree 94%
  - Minimal/No inflammatory response 95%

Status of Articular Cartilage at Second Look Procedure

- Improvement/No change in Outerbridge score 82%
- Improvement in degenerative disease 23%
- Worsening of articular cartilage disease 18%

Additional Procedures

- A total of 162 patients with device had 2nd look arthroscopy, during which needle biopsy was performed
- At 60 months, 27 CS patients and 20 control patients had additional procedures on the study knee
- 7 had additional procedures at 2nd arthroscopy such as debridement

Summary

- Scientific evidence of the safety and effectiveness of this device is difficult to obtain from the clinical data presented because of the following limitations:
  - Definition of “acute” and “chronic” used in the study arms
  - A non-homogenous control cohort in the “control” arm of the study
  - Analysis using pooled data from the two arms of the study

Summary (cont'd)

- Missing data at 24 months
- Failure to meet the predetermined study success
- Use of Tegner index as an new endpoint
- Lack of standard quantitative definition of adverse events
- Non-standardized method of measuring tissue gain
- Incomplete explant analysis
- Analyses conducted at different time points

ReGen Collagen Scaffold Statistical Considerations

Scott W. Miller, PhD
Division of Biostatistics
OSB, CDRH, FDA

Overview

- Clinical data design
  - Feasibility study
  - Clinical trial
- Clinical data results
  - Feasibility study
  - Clinical trial
- Potential issues with analysis

Feasibility Study Design

- 8 subjects treated with collagen scaffold
- No control arm
- Clinical outcomes published
  - 24 months post-surgery[1]
  - 70 months post-surgery[2]

1 Rodkey WG, Steadman JR, and Li S-T. "A clinical study of collagen meniscus implants to restore the injured meniscus". *Clinical Orthopaedics and Related Research*. 1999;**367S**:S281-S292.

2 Steadman JR, and Rodkey WG. "Tissue-engineered collagen meniscus implants: 5- to 6-year feasibility study results". *Arthroscopy: The Journal of Arthroscopic and Related Surgery*. 2005;**21**(5):515-525.

Clinical Trial Design

- The predominant source of clinical data is a trial conducted under IDE G920211
- The sponsor states that only data pertaining to device-treated subjects is relevant
  - Presents device-treated subjects as case histories
  - Omits control subject data
- FDA believes that this data arose from a clinical trial, and that the protocol is relevant

Clinical Trial Design (cont'd)

- Multi-center, randomized (1:1), un-blinded clinical trial
- Two treatment arms
  - Partial menisectomy plus collagen scaffold (CS)
  - Partial menisectomy (PM)
- 26 investigators / 16 centers
- 2 protocols, different subject cohorts
  - Acute (0 prior surgeries)
  - Chronic (1-3 prior surgeries)
- Surgery, then assessed over time
  - Baseline, 6 weeks, 3, 6, 12, 24 months
  - Primary end-point: 24 months post-surgery

Concerns with Clinical Trial Design

- Un-blinded; subjects aware of treatment allocation prior to surgery. Differential pre-operative dropout
  - Possible selection bias
  - Potential bias in patient reported outcomes
- Different post-surgical recovery regimens
  - Possible confounding of treatment effect

Patient Accounting

- 494 enrolled
- 183 excluded
  - 132 did not meet inclusion/exclusion criteria
  - 49 refused to participate
  - 2 other reasons
- 311 treated
  - 160 CS*
  - 151 PM

Acute		Chronic	
157		154	
CS	PM	CS	PM
75	82	85	69

*162 subjects treated with CS, but 2 deaths were excluded from JBJS analysis

Refusal to Participate

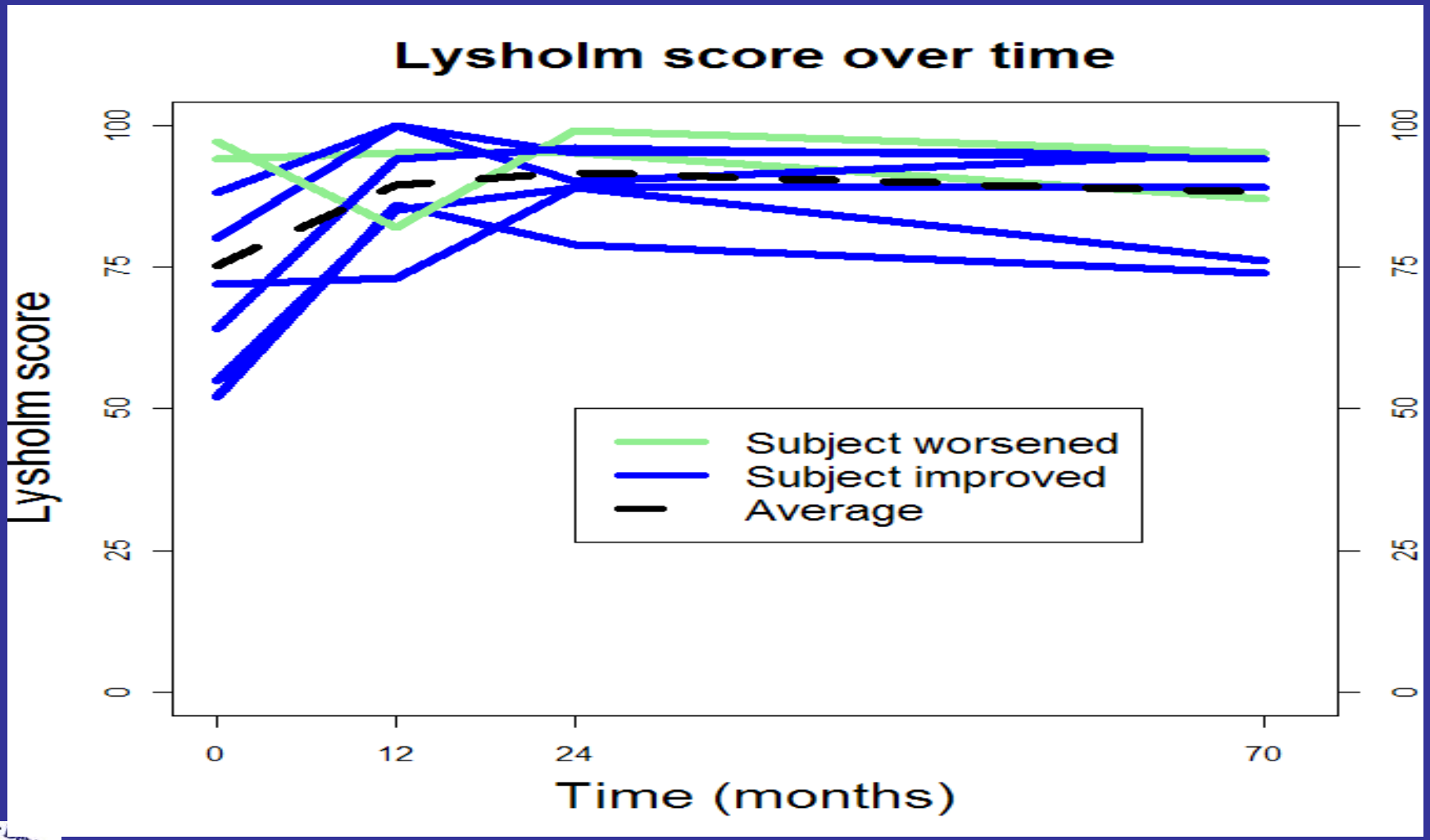
- Reason not recorded for all, but some listed as “subject did not want to be a control”
- More PM subjects withdrew; particularly in chronic arm
- This may represent evidence of patient self selection bias
- Remaining device-treated subjects may be more inclined to believe that the device is effective
- Potential for bias in patient-reported outcomes

Acute		Chronic	
14		35	
CS	PM	CS	PM
5	9	10	25

Patient Disposition

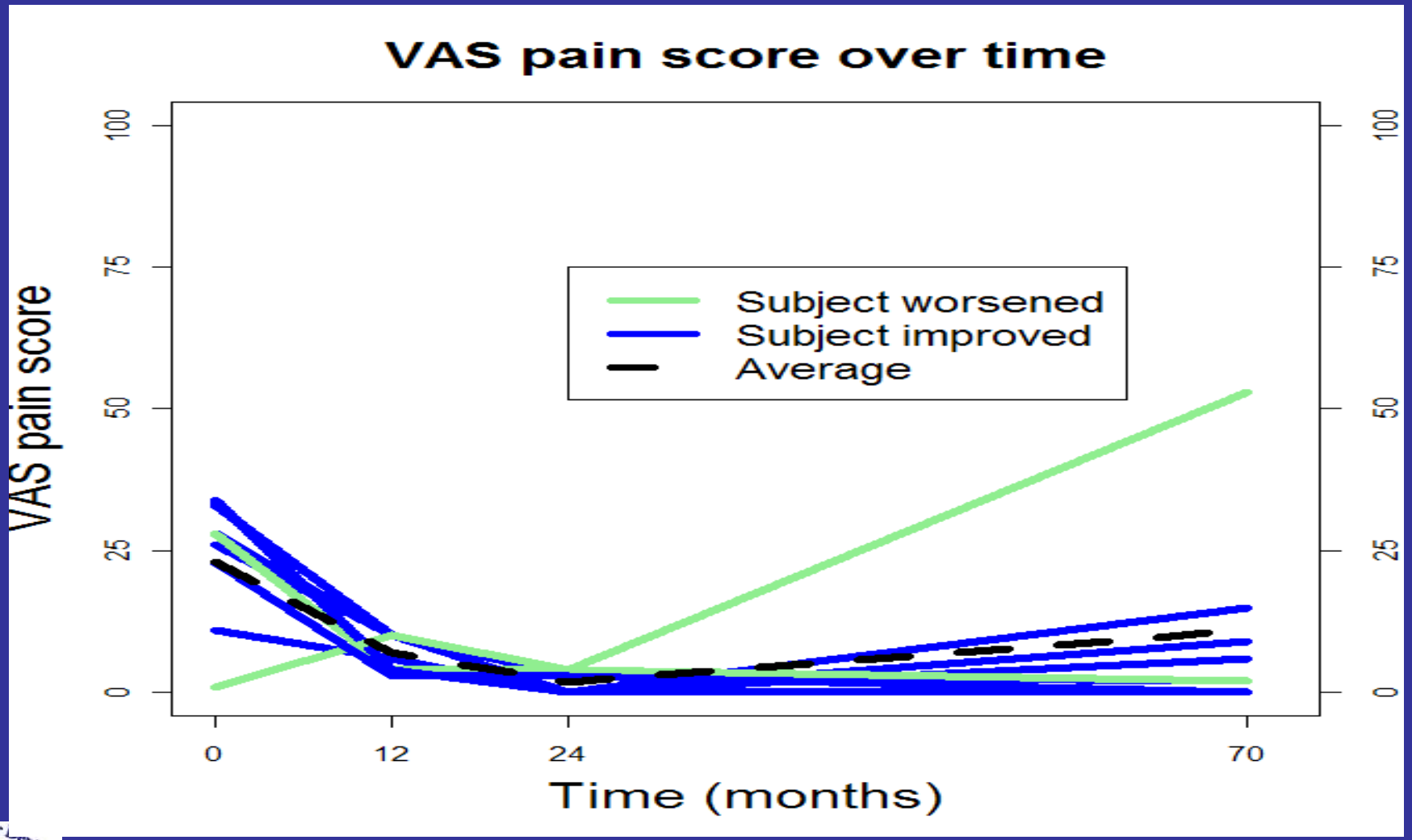
	Baseline	24 months
CS	162	132 (82%)
PM	151	128 (85%)

Feasibility Study Results: Lysholm



75	92	88
Mean		

Feasibility Study Results: VAS Pain



23	2	11
Mean		

Clinical Trial Primary Outcome

- Primary outcome: composite variable
  - Success if at least 2 of following successes:
  - Pain (100 mm Visual Analog Scale)
    - 20% decrease in average of
      - Highest activity
      - Activities of daily living
      - Rest
  - Function (Lysholm score)
    - If baseline <80, improve ≥20%
    - If baseline ≥ 80, final score ≥ 95
  - Patient function self-assessment
    - If baseline is ‘normal’ or ‘nearly normal’, no worsening
    - If not, improve at least one grade from baseline

14 Pre-Defined Secondary Endpoints

- Synovial fluid
- Redness
- Skin/superficial wound healing
- Range of motion
- Thigh girth
- Functional evaluation
- Tegner activity scale
- Radiographic evaluation
- Gross appearance of regeneration
- Implant appearance
- Implant-host stability
- Presence of loose bodies or fraying
- Implant-host junction
- Presence of inflammatory response

Primary Endpoints: Pain 100 mm VAS

Treatment group	Pre-operative (baseline) group mean	24 months post-operative group mean	Within subject mean improvement from baseline
CS (N=162)	35 ± 24 (N=155)	11 ± 16 (N=132)	22 ± not reported (N=131; 81%)
PM (N=151)	37 ± 24 (N=149)	11 ± 16 (N=130)	25 ± not reported (N=131; 87%)

Mean ± Standard deviation

Scale goes from [0-100]: higher is worse pain

Primary Endpoints: Function Lysholm

Treatment group	Pre-operative (baseline) group mean	24 months post-operative group mean	Within subject mean change from baseline
CS (N=162)	63 ± 19 (N=156)	86 ± 17 (N=133)	23 ± not reported (N=133; 82%)
PM (N=151)	59 ± 21 (N=149)	86 ± 15 (N=130)	27 ± not reported (N=130; 86%)

Mean ± Standard deviation

Scale goes from [0-100]: higher is better function

Primary Endpoints: Patient Function Satisfaction

Treatment group	Status	Pre-operative (baseline)	24 months
		N=156	N=133; 82%
CS (N=162)	Normal	6 (4%)	62 (47%)
	Nearly normal	62 (40%)	62 (47%)
	Abnormal	81 (52%)	8 (6%)
	Severely abnormal	7 (4%)	1 (1%)
		N=151	N=130; 86%
PM (N=151)	Normal	1 (1%)	56 (43%)
	Nearly normal	54 (36%)	65 (50%)
	Abnormal	72 (48%)	7 (5%)
	Severely abnormal	24 (16%)	2 (2%)

Tegner Index

- Tegner Index (TI)[3]:

$$TI = \frac{\text{Activity gain during study}}{\text{Activity loss due to injury}} = \frac{T_{\text{Follow-up}} - T_{\text{Pre-surgery}}}{T_{\text{Pre-injury}} - T_{\text{Pre-surgery}}}$$

- Not pre-defined in protocol
- Not used by other investigators/articles
- Pre-injury value based on subject recall at baseline
- Follow-up time potentially different for each subject
- Undefined if no loss due to injury (division by zero)
- Unknown statistical distribution, standard error
- Unknown minimal clinically significant difference
- Unknown psychometric properties

3 Rodkey WG, Steadman JR, Briggs KK. "Development and use of the 'Tegner Index' to assess effectiveness of arthroscopic treatment of the knee meniscus on return to activity." *European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA)*, Innsbruck, Austria, May 24-27, 2006

Tegner Index Results

- Mean Tegner Index
- Standard deviation not presented
- Most recent follow-up
- Sponsor states that the chronic comparison is statistically significant
- However, no way for FDA to independently verify
- No exploration of a population by treatment interaction
- In the absence of such an interaction, the main effect of treatment (CS vs. PM) is more appropriate

Chronic		Acute	
CS	**PM**	**CS**	**PM**
42%	29%	41%	41%

Tegner Index: Interpretation

- Hypothetical Tegner scores: (pre-injury, pre-surgery, post-surgery)
  - Subject 1: 8, 4, 5
  - Subject 2: 6, 4, 5
  - Subject 3: 5, 4, 5
  - Subject 4: 4, 4, 5

- Subject 1
  - Raw change from baseline: 5-4=+1
  - Tegner Index: (5-4)/(8-4)=1/4=+0.25
- Subject 2
  - Raw change from baseline: 5-4=+1
  - Tegner Index: (5-4)/(6-4)=1/2=+0.50
- Subject 3
  - Raw change from baseline: 5-4=+1
  - Tegner Index: (5-4)/(5-4)=1/1=+1
- Subject 4
  - Raw change from baseline: 5-4=+1
  - Tegner Index: (5-4)/(4-4)=1/0=undefined

12 Month Re-look Assessment

- Tissue in-growth assessed in 141/162 (89%) of device-treated subjects only
- Control subjects not assessed*
- Unblinded assessment
- Tissue in-growth estimation was subjective
- Thus, even if no tissue re-growth in controls, the measurement would have had some uncertainty had it been assessed

*Assumes no tissue re-growth after partial menisectomy
Sponsor cites literature supporting this assumption

12 Month Re-look Assessment

	Treatment group	N observed (missing)	Percent tissue remaining (SD)	N observed (missing)	Percent tissue total at re-look (SD)
Acute	CS	75 (0)	52 (20)	65 (10)	74 (17)
	PM	83 (1)	59 (20)	NA*	59*
Chronic	CS	87 (0)	36 (20)	76 (11)	73 (21)
	PM	66 (1)	40 (22)	NA*	40*

Trial Analysis Issues

- Very limited subject-level data was submitted
- Composite endpoint not presented
- Pain, function, patient self-assessment
  - Presented as means
  - Not as proposed success/failure based on baseline value
- VAS, Lysholm both have scales from [0,100]
  - Analyzing using t-tests may not be appropriate due to truncated range of scales
- Subjects not blinded
  - Possible bias in patient-reported endpoints

Trial Analysis Issues (cont'd)

- Randomization was stratified by clinical investigator, but the analyses presented did not account for it.
  - Potential for significant treatment-by-center interaction remains a possibility
  - If present, there may be important differences regarding aspects of device usage which FDA is unaware of

Trial Analysis Issues (cont'd)

- Missing data at 24 months ignored (completers only)
  - Possible source of bias
  - No imputation for missing data
  - No sensitivity analysis to examine how robust the observed results are
  - Alternative approach was to use "most recent follow-up" for each subject
  - Difficulty in interpreting data combined from subjects assessed at potentially widely different time-points
- No adjustment for multiple comparisons / hypothesis tests
  - Multiple hypotheses tests conducted
  - Some tests not pre-specified
  - Inflation of type I error

Summary

Predicate Devices

- Surgical meshes
  - Variety of anatomical locations
  - No intra-articular joint spaces
  - No fully weight bearing joints
- Differences in technological characteristics
  - Material
  - Shape
  - Size/dimensions
  - Anatomical location
- Scientific considerations of predicate devices

Preclinical Data

- It is unclear from the mechanical testing whether the CS device can withstand loading from weight bearing in the knee joint
- The animal study data are unclear, difficult to ascertain whether:
  - Tissue ingrowth quantity and quality are sufficient to withstand the mechanical demands of the knee
  - The CS device or newly formed tissue will damage articular cartilage of the tibia or femur over time

Clinical Data

- Data arose from a clinical trial, and the protocol is relevant
- Questions are about the data submitted
- Failure to meet the predetermined study success criteria
- Pooled acute and chronic patient populations
- Safety
  - Lack of standard quantitative definition of adverse events
  - Comparison to other meshes not relevant
- Effectiveness – Clinical meaning of Tegner Index unclear
- Analyses conducted at different time points